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(71) Applicant *(for all designated States except US)*: BEECHAM GROUP PLC [GB/GB]; Four New Horizons Court, Harlequin Avenue, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : BATESON, John, Hargreaves [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB). BURTON, George [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betworth, Surrey RH3 7AJ (GB). FELL, Stephen, Christopher, Martin [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB).

(74) Agent: WHITE, Susan, Mary; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

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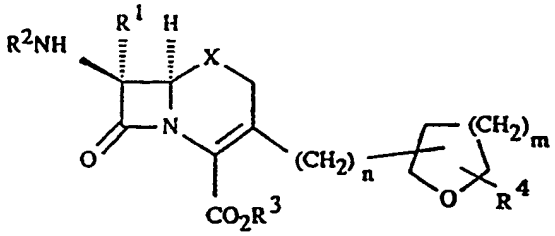

(I)

(57) Abstract

Compounds of formula (I) or a salt thereof, processes for their preparation, their use as antibiotics, and intermediates thereto, wherein R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group, in particular that of an antibacterially active cephalosporin; CO_2R^3 is a carboxy group or a carboxylate anion, or R^3 is a readily removable carboxy protecting group; R^4 represents up to four substitutents which may be the same or different; m is 1 or 2; and n is 1.

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CEPHALOSPORINS AND HOMOLOGUES, PREPARATIONS AND PHARMACEUTICAL COMPOSITIONS.

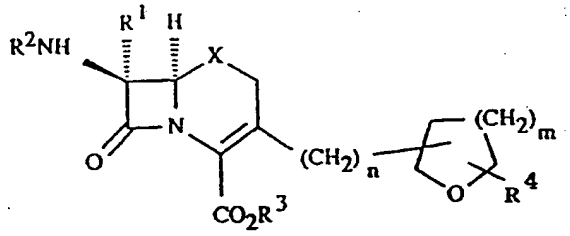
This invention relates to novel β-lactam containing compounds, their preparation and their use, and in particular to a novel class of cephalosporins. These compounds have antibacterial properties, and are therefore of use in the treatment of bacterial infections in humans and animals caused by a wide range of organisms.

GB 1 405 758 (Beecham Group Ltd) discloses the compound 3-(2-tetrahydropyranylmethyl)-7-(2-thienylacetamido)-3-cephem-4-carboxylic acid and records its in vitro activity (MIC) against five typical Gram-positive bacteria. Intermediates thereto in the form of the t-butyl-4-carboxylate and the corresponding 7-amino-and 7-triphenylmethylamino- t-butyl esters are also disclosed.

Nayler J.H.C. et al. (Journal of Medicinal Chemistry, 1977, Vol 20,) discloses the compound 3-(2-tetrahydropyranyl-methyl)-7β-(D-α-phenylglycyl)aminoceph-3-em-4-carboxylic acid and records its in vitro activity (MIC) against two Gram-positive and five Gram-negative bacteria. Intermediates thereto in the form of the 7-amino- and 7β-(N-t-butoxycarbonyl-D-α-phenylglycyl)amino-t-butyl-4-carboxylate derivatives are also disclosed.

We have now found a particular class of cephalosporins bearing a cyclic ether substituent at the 3-position of the cephalosporin nucleus that possesses prolonged and high levels of antibacterial activity, and shows good absorption both parentally and orally, especially orally.

The present invention provides a compound of formula (I) or a salt thereof:



(I)

wherein

R^1 is hydrogen, methoxy or formamido;

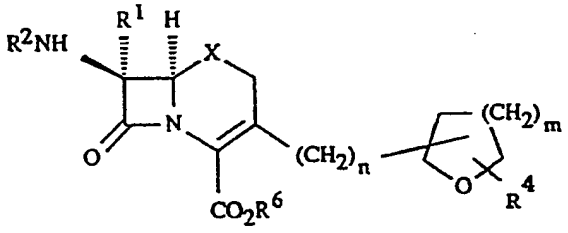
R^2 is an acyl group, in particular that of an antibacterially active cephalosporin;

CO_2R^3 is a carboxy group or a carboxylate anion, or R^3 is a readily removable carboxy protecting group (such as a pharmaceutically acceptable in-vivo hydrolysable ester group); R^4 represents up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent; X is S, SO, SO_2, O or CH_2; m is 1 or 2; and n is 1, subject to the proviso that when R^1 is hydrogen, X is S and the 3-position substituent is unsubstituted tetrahydropyran-2-ylmethyl (m=2), then, when R^3 is hydrogen, R^2 is not 2-thienylacetyl or D-α-aminophenylacetyl, and when R^3 is t-butyl, R^2 is not 2-thienylacetyl, D-α-aminophenylacetyl or N-t-butoxycarbonyl-D-α-amino-phenylacetyl.

The bonding carbon atom of the cyclic ether moiety which links the ring to the cephalosporin nucleus is generally asymmetric. The present invention includes either stereoisomer, as well as mixtures of both isomers.

In compounds of formula (I) wherein R^1 is formamido, the formamido group can exist in conformations wherein the hydrogen atoms of the -NH-CHO moiety are cis- or trans-; of these the cis conformation normally predominates.

Since the β-lactam antibiotic compounds of the present invention are intended for use as therapeutic agents in pharmaceutical compositions, it will be readily appreciated that preferred compounds within formula (I) are pharmaceutically acceptable, i.e. are compounds of formula (Ia) or pharmaceutically acceptable salts or pharmaceutically acceptable in vivo hydrolysable esters thereof:



(Ia)

wherein R^1, R^2, R^4, m, n and X are as defined with respect to formula (I) and the group CO_2R^6 is CO_2R^3 where CO_2R^3 is a carboxy group or a carboxylate anion.

Accordingly, the present invention provides a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use as a therapeutic agent, and in particular an in vivo hydrolysable ester

thereof for use as an orally administrable therapeutic agent.

The present invention further provides a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use in the treatment of bacterial infections, more particularly an in vivo hydrolysable ester thereof for use in the oral treatment of bacterial infections.

The present invention also includes a method of treating bacterial infections in humans and animals which comprises the administration of a therapeutically effective amount of an antibiotic compound of this invention of the formula (Ia) or a pharmaceutically acceptable in vivo hydrolysable ester thereof, in particular the oral administration of a therapeutically effective amount of an in vivo hydrolysable ester.

In addition, the present invention includes the use of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for the manufacture of a medicament for the treatment of bacterial infections, in particular the use of an in vivo hydrolysable ester for the manufacture of a medicament for the oral treatment of bacterial infections.

Those compounds of the formula (I) wherein R^3 is a readily removable carboxy protecting group other than a pharmaceutically acceptable in vivo hydrolysable ester or which are in non-pharmaceutically acceptable salt form are primarily useful as intermediates in the preparation of compounds of the formula (Ia) or a pharmaceutically acceptable salt or pharmaceutically acceptable in vivo hydrolysable ester thereof.

Suitable readily removable carboxy protecting groups for the group R^3 include groups forming ester derivatives of the carboxylic acid, including in vivo hydrolysable esters. The derivative is preferably one which may readily be cleaved in vivo.

It will be appreciated that also included within the scope of the invention are salts and carboxy-protected derivatives, including in vivo hydrolysable esters, of any carboxy groups that may be present as optional substituents in compounds of formula (I) or (Ia). Also included within the scope of the invention are acid addition salts of any amino group or substituted amino group that may be present as optional substituents in compounds of formula (I) or (Ia).

Suitable ester-forming carboxyl-protecting groups are those which may be removed under conventional conditions. Such groups for R^3 include benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, p-toluenesulphonylethyl, methoxymethyl, a silyl, stannyl or phosphorus- containing group, an oxime radical of formula $-N=CHR^7$ where R^7 is aryl or heterocyclic, or an in vivo hydrolysable ester radical such as defined below.

When used herein the term 'aryl' includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from halogen, mercapto, C_{1-6} alkyl, phenyl, C_{1-6} alkoxy, hydroxy(C_{1-6})alkyl, mercapto(C_{1-6})alkyl, halo(C_{1-6}) alkyl, hydroxy, amino, nitro, carboxy, C_{1-6} alkylcarbonyloxy, alkoxycarbonyl, formyl, or C_{1-6} alkylcarbonyl groups.

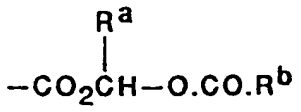
The terms 'heterocyclyl' and 'heterocyclic' as used herein include aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three groups selected from halogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. The term 'heteroaryl' refers to heteroaromatic heterocyclic rings. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

When used herein the terms 'alkyl' alkenyl, alkynyl and 'alkoxy' include straight and branched chain groups containing from 1 to 6 carbon atoms, such as methyl, ethyl, propyl and butyl. A particular alkyl group is methyl.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine.

A carboxyl group may be regenerated from any of the above esters by usual methods appropriate to the particular R^3 group, for example, acid- and base- catalysed hydrolysis, or by enzymically-catalysed hydrolysis, or by hydrogenolysis under conditions wherein the remainder of the molecule is substantially unaffected.

Examples of suitable pharmaceutically acceptable in vivo hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Suitable ester groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):



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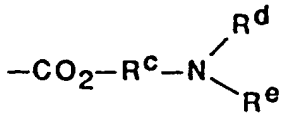

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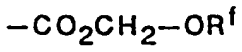

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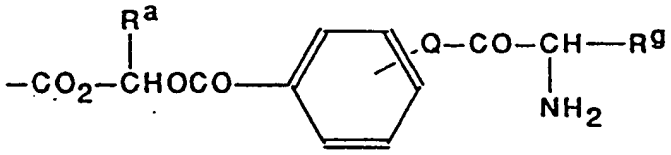

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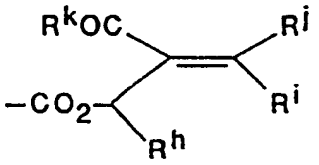


(v)

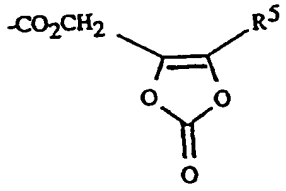
wherein R^a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, methyl, or phenyl, R^b is C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, benzyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyloxy, C_{1-6} alkyl C_{3-7} cycloalkyl, 1-amino C_{1-6} alkyl, or 1-(C_{1-6} alkyl)amino C_{1-6} alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents C_{1-6} alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent C_{1-6} alkyl; R^f represents C_{1-6} alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, C_{1-6} alkyl, or C_{1-6} alkoxy; Q is oxygen or NH; R^h is hydrogen or C_{1-6} alkyl; R^i is hydrogen, C_{1-6} alkyl optionally substituted by halogen, C_{2-6} alkenyl,

C_{1-6} alkoxycarbonyl, aryl or heteroaryl; or R^h and R^i together form C_{1-6} alkylene; R^j represents hydrogen, C_{1-6} alkyl or C_{1-6} alkoxycarbonyl; and R^k represents C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy or aryl.

Examples of suitable in vivo hydrolysable ester groups include, for example, acyloxyalkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; dialkylaminoalkyl especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-(alkoxycarbonyl)-2-alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl; and esters linked to a second β-lactam antibiotic or to a β-lactamase inhibitor.

A preferred in vivo hydrolysable ester group is the pivaloyloxymethyl ester.

A further suitable pharmaceutically acceptable in vivo hydrolysable ester group is that of the formula:



wherein R^5 is hydrogen, C_{1-6} alkyl or phenyl.

Suitable pharmaceutically acceptable salts of the carboxy group of the compound of formula (I) include metal salts, eg aluminium, alkali metal salts such as sodium or potassium,

especially sodium, alkaline earth metal salts such as calcium or magnesium, and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy-lower alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tris-(2-hydroxyethyl)- amine, cycloalkylamines such as dicyclohexylamine, or with procaine, dibenzylamine, N,N-dibenzylethylene- diamine, 1-ephenamine, N-methylmorpholine, N-ethylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, ethylenediamine, or bases of the pyridine type such as pyridine, collidine or quinoline, or other amines which have been used to form salts with known penicillins and cephalosporins. Other useful salts include the lithium salt and silver salt. Salts within compounds of formula (I), may be prepared by salt exchange in conventional manner.

In compounds of formula (I) or (Ia), the group X may be sulphur or an oxidised sulphur atom, i.e. a sulphoxide (SO) or sulphone (SO_2) group. When X is a sulphoxide group it will be understood that α- and β-isomers may exist; both such isomers are encompassed within the scope of the present invention.

Preferably X is sulphur.

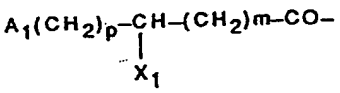
Advantageously, R^1 is hydrogen.

Suitably, the cyclic ether at the 3-position of the cephalosporin nucleus is unsubstituted or substituted by up to three substituents, R^4, selected from C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkoxycarbonyl C_{1-6} alkoxy C_{1-6} alkyl, and C_{1-6} alkanoyloxy C_{1-6} alkyl. Preferably the cyclic ether at the 3-position of the cephalosporin nucleus is unsubstituted.

Preferably m is 1.

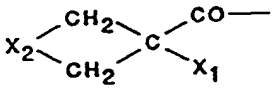
Preferably the cyclic ether is bonded to the cephalosporin nucleus at a ring carbon adjacent to the oxygen heteroatom.

Suitable acyl groups R^2 include those of formulae (a) - (f):

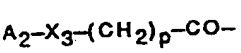


(a)

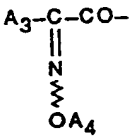
(b)



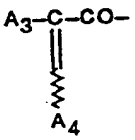
(c)



(d)



(e)



(f)

wherein p is 0, 1 or 2; m is 0, 1 or 2; A_1 is C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-6} cycloalkyl, cyclohexenyl, cyclohexadienyl, an aromatic (including heteroaromatic) group, such as phenyl, substituted phenyl, thienyl, pyridyl, or an optionally substituted thiazolyl group, a C_{1-6} akylthio group or C_{1-6} alkyloxy; X_1 is a hydrogen or halogen atom, a carboxylic acid, carboxylic ester, sulphonic acid, azido, tetrazolyl, hydroxy, acyloxy, amino, ureido, acylamino, heterocyclylamino, guanidino or acylureido group;

A_2 is an aromatic group, for example a phenyl, 2,6-dimethoxyphenyl,2-alkoxy-1-naphthyl, 3-arylisoxazolyl, or a 3-aryl-5-methylisoxazolyl group, such as 3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl; a substituted alkyl group; or a substituted dithietane; X_2 is a $-CH_2OCH_2-$, $-CH_2SCH_2-$ or alkylene group; X_3 is an oxygen or sulphur atom; A_3 is an aryl or heteroaryl group such as phenyl, substituted phenyl, furyl, aminothiazolyl or aminothiadiazolyl in which the amino group is optionally protected; and A_4 is hydrogen, C_{1-6}alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-6})alkyl, C_{1-6} alkoxycarbonyl(C_{1-6}) alkyl, C_{2-6} alkenyl, carboxy(C_{1-6})alkyl, C_{2-6} alkynyl, aryl or C_{1-6}alkyl substituted by up to three aryl groups.

The term 'heteroaryl' as used herein means a heteroaromatic heterocyclic ring or ring system, suitably having 5 or 6 ring atoms in each ring.

Suitably when R^2 is a group (a), A_1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, cyclohexenyl, cyclohexadienyl, phenyl, substituted phenyl such as hydroxyphenyl, thienyl or pyridyl; and X_1 is a hydrogen or halogen atom, or a carboxy, carboxylic ester, azido, tetrazolyl, hydroxy, acyloxy, optionally protected amino, ureido, guanidino or acylureido group.

Suitably when R^2 is a group of formula (d), A_2 is phenyl, X_3 is oxygen and p is 0.

Alternatively when R^2 is a group of formula (e) or (f) suitable values for the group A_3 include those commonly found in antibacterially active cephalosporins containing a hydroxyimino, substituted hydroxyimino or vinyl group in the side chain attached to position 7 of the cephalosporin nucleus, for example phenyl, thien-2-yl, thien-3-yl,

fur-2-yl, fur-3-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 5-amino-1,2,4-thiadiazol-3-yl and 2-aminothiazol-4-yl in each of which the amino group is optionally protected.

Preferred groups for A_3 include phenyl, 2-aminothiazol-4-yl, fur-2-yl, thien-2-yl, 2-(2-chloroacetamido)thiazol-4-yl, 2-tritylamino-thiazol-4-yl, 5-amino-1,2,4-thiadiazol-3-yl and 4-aminopyrimid-2-yl.

In compounds of formula (Ia), a particularly preferred group for A_3 is 2-aminothiazol-4-yl.

Suitable values for the group A_4 include hydrogen, methyl, ethyl, cyclopropylmethyl, triphenylmethyl (trityl), cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, carboxymethyl, carboxypropyl and t-butoxycarbonylmethyl.

Preferred values for A_4 in compounds of formula (Ia) include methyl and hydrogen.

It will be appreciated that compounds of the invention wherein R^2 is a group of formula (e) (or (f)) can exist as syn and anti (or E and Z) isomers or mixtures thereof. Both isomers are encompassed within the scope of this invention.

Preferably the compounds of the invention wherein R^2 is a group of formula (e) have the syn configuration (i.e. have the group OA_4 syn to the amide linkage) or are enriched in that isomer.

Similarly, when R^2 is a group of formula (f), the group A_4 is preferably cis to the amide linkage, i.e. when group (f) is 2-amino-thiazol-4-yl, the Z-configuration is preferred.

Certain compounds of the invention include an amino group which may be protected. Suitable amino protecting groups are those well known in the art which may be removed under conventional conditions without disruption of the remainder of the molecule.

Examples of amino protecting groups include C_{1-6} alkanoyl; benzoyl; benzyl optionally substituted in the phenyl ring by one or two substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, halogen, or nitro; C_{1-4} alkoxycarbonyl; benzyloxycarbonyl or trityl substituted as for benzyl above; allyloxycarbonyl,trichloroethoxycarbonyl or chloroacetyl.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Since the antibiotic compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 95% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain

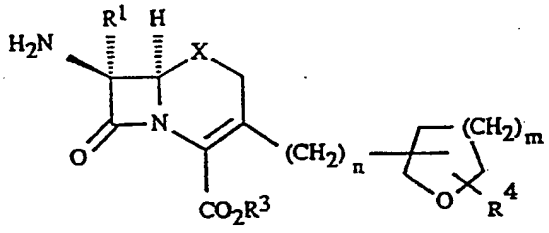
at least 1%, more suitably at least 5% and preferably from 10 to 49% of a compound of the formula (I) or salt thereof.

Specific compounds within this invention of formula (Ia) include the following pharmaceutically acceptable carboxylic acids, salts and in-vivo hydrolysable esters:

sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate; and

pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate.

The present invention further provides a process for the preparation of a compound of formula (I), which process comprises treating a compound of formula (II) or a salt thereof:



(II)

wherein R^1, CO_2R^3, R^4, m, n and X are as hereinbefore defined, wherein any reactive groups may be protected, and wherein the amino group is optionally substituted with a group which permits acylation to take place; with an N-acylating derivative of an acid of formula (III):

R^2OH (III)

wherein R^2 is as defined with respect to formula (I) and wherein any reactive groups may be protected; and thereafter, if necessary or desired, carrying out one or more of the following steps:

i) removing any protecting groups;

ii) converting the group CO_2R^3 into a different group CO_2R^3;

iii) converting the group R^2 into a different group R^2;

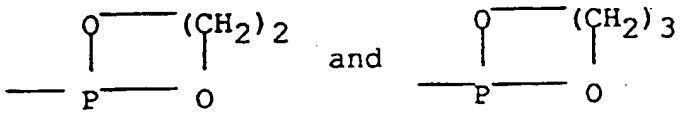
iv) converting the group X into a different group X;

v) converting the product into a salt.

Acids of formula (III) may be prepared by methods known in the art, or methods analogous to such processes. Suitable processes include those described, for example, in UK Patent 2 107 307 B, UK Patent Specification No. 1,536,281, and U.K. Patent Specification No. 1,508,064.

Suitable groups which permit acylation to take place and which are optionally present on the amino group of the starting material of the formula (II) include N-silyl, N-stannyl and N-phosphorus groups, for example trialkylsilyl groups such as trimethylsilyl, trialkyltin groups such as tri-n-butyltin, groups of formula $-P.R^{20}R^{21}$ wherein R^{20} is an alkyl, haloalkyl, aryl, aralkyl, alkoxy, haloalkyl, aryl, aralkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy or

dialkylamino group, R^{21} is the same as R^{20} or is halogen or R^{20} and R^{21} together form a ring; suitable such phosphorus groups being $-P(OC_2H_5)_2$, $-P(C_2H_5)_2$,



A group which may optionally be introduced onto the amino group in the compound of formula (II) is trimethylsilyl.

Advantageously the silylation reaction may be carried out in situ, prior to the acylation reaction, with a silylating agent that does not require concomitant addition of base. Suitable silylating agents include, for example, N-(trimethylsilyl)-acetamide, N,O-bis-(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)-trifluoroacetamide, N-methyl-N-trimethylsilylacetamide, N-methyl-N-trimethylsilyl-trifluoroacetamide, N,N'-bis(trimethylsilyl)urea, and N,O-bis(trimethylsilyl)carbamate. A preferred silylating agent is N,O-bis(trimethylsilyl)acetamide. The silylation reaction may suitably be carried out in an inert, anhydrous organic solvent such as dichloromethane at room temperature or at an elevated temperature, for example 30 - 60°C, preferably 40 - 50°C.

The above process may optionally be carried out in the presence of a small quantity, for example 0.1 equivalents, of a silyl halide, for example a tri(C_{1-6})alkylsilyl halide, especially trimethylsilyl chloride.

A reactive N-acylating derivative of the acid (III) is employed in the above process. The choice of reactive

derivative will of course be influenced by the chemical nature of the substituents of the acid.

Suitable N-acylating derivatives include an acid halide, preferably the acid chloride or bromide or alternatively a symmetrical or mixed anhydride. The acylation may be effected in the presence of an acid binding agent for example, tertiary amine (such as pyridine or dimethylaniline), molecular sieves, an inorganic base (such as calcium carbonate or sodium bicarbonate) or an oxirane, which binds hydrogen halide liberated in the acylation reaction. The oxirane is preferably a (C_{1-6})-1,2-alkylene oxide - such as ethylene oxide or propylene oxide. The acylation reaction using an acid halide may be carried out at a temperature in the range -50°C to +50°C, preferably -20°C to +20°c, in aqueous or non-aqueous media such as water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, dichloromethane, 1,2-dichloroethane, or mixtures thereof. Alternatively, the reaction may be carried out in an unstable emulsion of water-immiscible solvent, especially an aliphatic ester or ketone, such as methyl isobutyl ketone or butyl acetate. The acylation with acid halide or anhydride is suitably carried out in the presence of a basic catalyst such as pyridine or 2,6-lutidine.

Acid halides may be prepared by reacting the acid (III) or a salt or a reactive derivative thereof with a halogenating (eg chlorinating or brominating) agent such as phosphorus pentachloride, thionyl chloride, oxalyl chloride or phosgene.

Suitable mixed anhydrides are anhydrides with, for example, carbonic acid monoesters, trimethyl acetic acid, thioacetic acid, diphenylacetic acid, benzoic acid, phosphorus acids (such as phosphoric, phosphorous, and phosphinic acids) or

aromatic or aliphatic sulphonic acids (such as p-toluenesulphonic acid or methanesulphonic acid).

Alternative N-acylating derivatives of acid (III) are the acid azide, or activated esters such as esters with 2-mercaptopyridine, cyanomethanol, p-nitrophenol, 2,4-dinitrophenol, thiophenol, halophenols, including pentachlorophenol, monomethoxyphenol, N-hydroxy succinimide, N-hydroxybenzotriazole, or 8-hydroxyquinoline; or amides such as N-acylsaccharins, N-acylthiazolidin-2-thione or N-acylphthalimides; or an alkylidene iminoester prepared by reaction of the acid (III) with an oxime.

Other reactive N-acylating derivatives of the acid (III) include the reactive intermediates formed by reaction in situ with a condensing agent such as a carbodiimide, for example, N,N'-diethyl-, dipropyl- or diisopropylcarbodiimide, N,N'-di-cyclohexyl-carbodiimide, or N-ethyl-N'-[3-(dimethylamino)propyl]- carbodiimide; a suitable carbonyl compound, for example, N,N'-carbonyldiimidazole or N,N'-carbonyldi- triazole; an isoxazolinium salt, for example, N-ethyl-5-phenylisoxazolinium-3-sulphonate or N-t-butyl-5-methylisoxazolinium perchlorate; or an N-alkoxycarbonyl 2-alkoxy-1,2-dihydroquinoline, such as N-ethoxycarbonyl 2-ethoxy-1,2-dihydroquinoline. Other condensing agents include Lewis acids (for example $BBr_3 - C_6H_6$); or a phosphoric acid condensing agent such as diethylphosphorylcyanide. The condensation reaction is preferably carried out in an organic reaction medium, for example, methylene chloride, dimethylformamide, acetonitrile, alcohol, benzene, dioxan or tetrahydrofuran.

A further method of forming the N-acylating derivative of the acid of formula (III) is to treat the acid of formula (III) with a solution or suspension preformed by addition of

a carbonyl halide, preferably oxalyl chloride, or a phosphoryl halide such as phosphorus oxychloride, to a halogenated hydrocarbon solvent, preferably dichloromethane, containing a lower acyl tertiary amide, preferably N,N-dimethylformamide. The N-acylating derivative of the acid of formula (III) so derived may then be caused to react with a compound of formula (II). The acylation reaction may conveniently be carried out at -40° to +30°C, if desired in the presence of an acid binding agent such as pyridine. A catalyst such as 4-dimethylaminopyridine may optionally also be added. A preferred solvent for the above acylation reaction is dichloromethane.

The optional reduction step, the optional conversion of R^2 to a different R^2, CO_2R^3 to a different CO_2R^3 and X to a different X, and the optional formation of a salt, may be carried out using methods well known in the art of cephalosporin and penicillin chemistry.

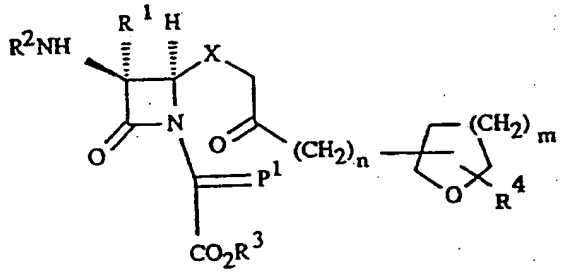
For example, when the group X is S, SO, or SO_2, the group X may be converted into a different group X by methods of oxidation or reduction well known in the art of cephalosporin and penicillin synthesis, as described, for example, in European Patent Application Publication No. 0 114 752. For example, sulphoxides (in which X is SO) may be prepared from the corresponding sulphide (in which X is S) by oxidation with a suitable oxidising agent, for example an organic peracid such as m-chloroperbenzoic acid.

A reduction step is generally effected by processes well known in the art of β-lactam chemistry, for example using phosphorus trichloride in dimethylformamide.

In the process described hereinabove, and in the process described hereinbelow, it may be necessary to remove protecting groups. Deprotection may be carried out by any

convenient method known in the art such that unwanted side reactions are minimised. Separation of unwanted by-products may be carried out using standard methods.

In a further process of the invention, compounds of formula (I) may be prepared by cyclising a compound of formula (IV):



(IV)

wherein X, R^1, R^2, R^4, m, n and CO_2R^3 are as hereinbefore defined and P' is a phosphorus residue; and thereafter if necessary or desired, carrying out one or more of the following steps:

i) removing any protecting groups;

ii) converting the group CO_2R^3 into a different group CO_2R^3;

iii) converting the group R^2 into a different group R^2;

iv) converting the group X into a different group X;

v) converting the product into a salt.

The cyclisation reaction is an intramolecular Wittig-type reaction and is typically carried out by heating the compound of formula (IV) in an organic solvent system, for

example in toluene, optionally in the presence of a suitable acid such as benzoic acid.

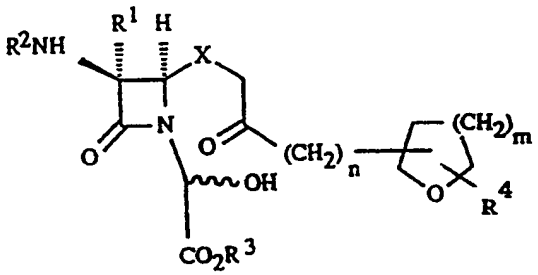
The phosphorus residue, P' is typically a trialkylphosphoranylidene residue, for example a C_{1-6} trialkylphosphoranylidene residue such as tri-n-butylphosphoranylidene, or a triarylphosphoranylidene residue such as triphenylphosphoranylidene.

Where R^2 in a compound of formula (I) is required to be different from the group R^2 in the compound of formula (IV), the conversion may be effected via the intermediacy of a compound of formula (II) which has an amino group at the 7-position of the cephalosporin nucleus.

An R^2 side-chain may be removed by the Delft procedure commonly used in β-lactam chemistry. Suitable reaction conditions include treatment with phosphorus pentachloride and N-methylmorpholine at reduced temperature.

Compounds of formula (II) are novel compounds and as such form part of the invention.

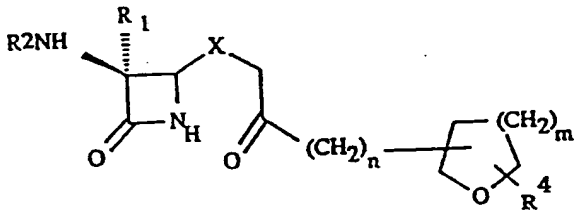
A compound of formula (IV) may be prepared from a compound of formula (V):



(V)

wherein X, R^1, R^2, R^4, m, n and CO_2R^3 are as hereinbefore defined, by reaction with a halogenating agent, suitably a chlorinating agent such as thionyl chloride, which reaction displaces the formula (V) hydroxyl group by halogen, suitably chloride, and is typically carried out at reduced temperature in an inert solvent, for example in tetrahydrofuran, in the presence of a base, typically a pyridine derivative such as 2,6-lutidine. Formation of the phosphorane may be effected by treatment of the halo-intermediate with an appropriate phosphine derivative, for example tri-n-butylphosphine or triphenylphosphine, suitably at ambient temperature in an inert solvent such as dioxan.

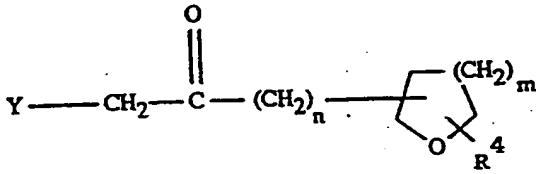
A compound of formula (V) may be prepared by reaction of a compound of formula (VI):



(VI)

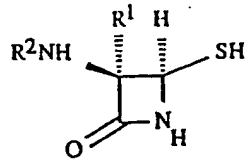
wherein X, R^1, R^2, R^4, m and n are as hereinbefore defined with an ester of glyoxylic acid ($OCHCO_2R^3$) in the presence of triethylamine.

In a typical preparation of a compound of formula (VI) in which X is sulphur, a compound of formula (VII):



(VII)

wherein Y is a leaving group and R^4, m and n are as hereinbefore defined is reacted with a compound of formula (VIII):

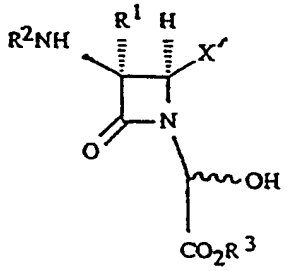


(VIII)

wherein R^1 and R^2 are as hereinbefore defined.

Suitably, a leaving group Y is halogen, for example chloro. The reaction may be carried out at ambient temperature in an inert solvent, for example acetone or dimethylformamide, in the presence for a base, for example potassium carbonate.

A compound of formula (V) may also be prepared by reaction of a compound of formula (IX):



(IX)

wherein R^1, R^2 and CO_2R^3 are as hereinbefore defined and X′ is an X-group precursor, with a compound of formula (VII) as hereinbefore defined.

In a typical preparation of a compound of formula (V) in which X is sulphur, a Y leaving group in a compound of formula (VII), suitably a halogen such as chloro or bromo, is displaced by an X′ mercapto group in a compound of formula (IX). The reaction may be carried out at ambient

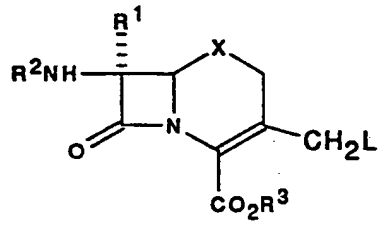
temperature in an inert solvent, for example acetone, with the addition of base, for example potassium carbonate, before work-up.

Azetidin-2-one compounds of formulae (VIII) and (IX) may be prepared according to known methods in heterocyclic synthetic chemistry and particularly by known methods in the art of β-lactam chemistry. For example a compound of formula (VIII) may be prepared according to the method of Osborne N.F. et al., J. Chem. Soc., Perkin Trans. I, 146, 1980.

A compound of formula (IX) in which X' is a mercapto group may be prepared by ring opening of a 4-thia-2,6-diazabicyclo [3.2.0]-hept-2-ene-7-one derivative according to the method of Masayuki Narisada et al., Tetrahedron Lett., 1755 (1978).

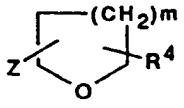
Compounds of formula (VII) are known compounds or may be prepared by standard methodology. For example, the compounds of formula (VII) in which Y is chloro or bromo may be prepared from the corresponding carboxylic acid (Y=COOH) via formation of the acid chloride followed by treatment with diazomethane and reaction of the resulting diazo compound with hydrogen chloride or hydrogen bromide.

In a further process of the invention, compounds of formula (I) may be prepared directly by organo-cuprate displacement of a leaving group at the 3-position of a compound of formula (X):



(X)

wherein R^1, R^2, CO_2R^3 and X are as hereinbefore defined and L is a leaving group, suitably a halogen, mesylate, triflate or fluorosulphonate leaving group, by reaction with a compound of formula (XI):



(XI)

wherein Z is an organo-cuprate group and R^4 and m are as hereinbefore defined.

A compound with a halogen 3-position leaving group, for example chloro, in which X is sulphur may be prepared by the procedure of Fujumoto K. et al., J. Antibiotics, 40, 370, (1987).

A compound with a 3-position leaving group, L, in which X is CH_2 may be prepared from the hydroxy intermediate, prepared as described by S. Uyeo and H. Ona, Chem. Pharm. Bull., 28, 1563, (1980).

It should be noted that in processes of this invention Δ^2-cephems may function as intermediates, in the synthetic sequences. Subsequent isomerisation steps by methods well known in cephalosporin chemistry will provide the Δ^3-cephems of the invention.

The present invention also provides a pharmaceutical composition which comprises a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

The compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as oral, topical or parenteral, especially oral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc,

polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed

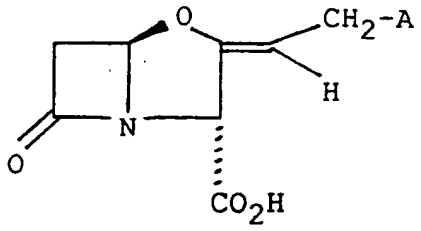
under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No unacceptable toxicological effects are expected when a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof is administered in the above-mentioned dosage range.

The compound of formula (Ia) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β-lactamase inhibitor may be employed.

Advantageously, the compositions also comprise a compound of formula (XIII) or a pharmaceutically acceptable salt or ester thereof:

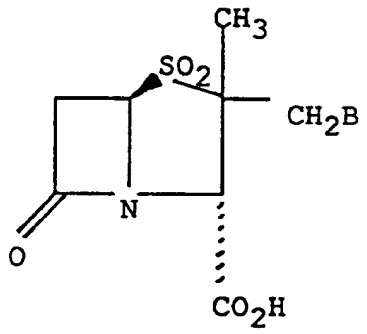


(XIII)

wherein

A is hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, mono- or di-hydrocarbyl- substituted amino, or mono- or di-acylamino; an optionally substituted triazolyl group; or an optionally substituted tetrazolyl group as described in EP-A-0 053 893.

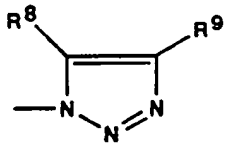
A further advantageous composition comprises a compound of formula (Ia) or a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable ester thereof together with a compound of formula (XIV) or a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable ester thereof:



(XIV)

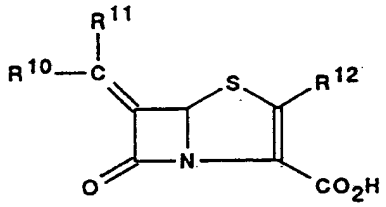
wherein

B represents hydrogen, halogen or a group of formula:



in which R^8 and R^9 are the same or different and each represents hydrogen, C_{1-6} alkoxycarbonyl or carboxy, or a pharmaceutically acceptable salt thereof.

Further suitable β-lactamase inhibitors include 6-alkylidene penems of formula (XV):



(XV)

or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, wherein R^{10} and R^{11} are the same or different and each represents hydrogen, or a C_{1-10} hydrocarbon or heterocyclic group optionally substituted with a functional group; and R^{12} represents hydrogen or a group of formula R^{13} or $-SR^{13}$ where R^{13} is an optionally substituted C_{1-10} hydrocarbon or heterocyclic group, as described in EP-A-0 041 768.

Further suitable β-lactamase inhibitors include 6β-bromopenicillanic acid and pharmaceutically acceptable salts and in vivo hydrolysable esters thereof and 6β-iodopenicillanic acid and pharmaceutically acceptable salts and in vivo hydrolysable esters thereof described in, for example, EP-A-0 410 768 and EP-A-0 154 132 (both Beecham Group).

Such compositions of this invention which include a β-lactamase inhibitory amount of a β-lactamase inhibitor are formulated in a conventional manner using techniques and procedures per se known in the art.

The antibiotic compounds of the present invention are active against a wide range of organisms including both Gram-negative organisms such as E.coli and Gram-positive organisms such as S.aureus.

The following Examples illustrate the preparation of compounds of the invention and intermediates thereto. The following biological data illustrate the activity of a compound of the invention in the form of MIC values (minimum inhibitory concentration) against a sample E.coli organism (NCTC 10418) and a sample S.aureus organism (S.aureus Oxford).

Example 1

Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

(a) Tetrahydrofuran-2-ylacetic acid

Benzyl tetrahydrofuran-2-ylacetate (0.4g, K.T. Mead and B. Samuel, Tetrahedron Lett., 1988, 29, 6573), in tetrahydrofuran (THF) (10ml) was treated with 10% palladium on carbon catalyst (0.08g) and the mixture hydrogenolysed until there was no further uptake of hydrogen, and t.l.c. analysis showed no starting material. The catalyst was removed by filtration through Kieselguhr. The sufficiently pure title compound was obtained as a colourless, viscous oil on removal of solvent, (0.229g, 97%); $\nu_{max}(CH_2Cl_2)$ 3500-2700 (v.br), 1712cm^{-1}; $\delta_H(CDCl_3)$ 1.6-2.4 (4H, m), 2.44-2.89 (2H, m), 3.73-4.12 (2H, m), 4.22-4.51 (1H, m) and 11.09 (1H, br.s). [Mass spectrum:+ve ion (NH_3) MH^+ (131) and MNH_4^+ (148)].

(b) 2-(3-Chloro-2-oxoprop-1-yl)tetrahydrofuran

Tetrahydrofuran-2-ylacetic acid (4.572g) in dry dichloromethane (50ml) was treated with oxalyl chloride (6.7g, 4.6ml) and then 2-3 drops of dimethylformamide (DMF). After the initial effervescence had subsided the solution was left at ambient temperature for 1.5h. The solvent and excess oxalyl chloride were removed in vacuo and the resultant oil [ν_{max} (CH_2Cl_2) 1797cm^{-1}] redissolved in dichloromethane (20ml), and added dropwise to an ice bath cooled ethereal solution ofdiazomethane (ca.80mmol). T.l.c. analysis (50% ethyl acetate/hexane) showed the diazoketone as a single mobile spot. Hydrogen chloride was bubbled

through the solution until no more starting material was observed by t.l.c. Silica gel column chromatography afforded the title compound as a pale yellow oil, (1.833g, 32%); (Found: $(M-Cl)^+$, 127.0758. $C_7H_{11}O_2$ requires M, 127.0759); $\nu_{max}(CH_2Cl_2)$ 1736cm^{-1}; $\delta_H(CDCl_3)$ 1.46-1.60 (1H, m), 1.86-1.96 (2H, m), 2.07-2.18 (1H, m), 2.76 (1H, dd, J5.1, 15.6Hz), 2.85 (1H, dd, J7.4, 15.6Hz), 3.74 (1H, dd, J8.2, 15.2Hz), 3.87 (1H, dd, J6.8, 15.2Hz), 4.19 (2H, s) and 4.25 (1H, m).

(c) (3R,4R)-3-Phenoxyacetamido-4-[2-oxo-3-[(RS)-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-one

(3R,4R)-4-Mercapto-3-phenoxyacetamidoazetidin-2-one (2.76g) and the chloroketone prepared in Example 1(b), (1.48g) together in DMF (10ml) were treated with potassium carbonate (1.39g) at ambient temperature for about 2h. T.l.c. analysis showed loss of chloroketone. The solution was diluted with ethyl acetate and washed with water (3x) and brine, dried and concentrated. Flash chromatography on silica gel eluting with 80% ethyl acetate in hexane afforded the title compound as a mixture of diastereoisomers as a colourless foam, (2.37g, 60%); [Found: M^+, 378.1241. $C_{18}H_{22}N_2O_5S$ requires M, 378.1249); $\nu_{max}(CHCl_3)$ 3405, 3295(br), 1782, 1693 and 1600cm^{-1}; $\delta_H(CDCl_3)$ 1.49-1.57 (1H, m), 1.84-1.97 (2H, m), 2.02-2.14 (1H, m), 2.58, 2.67, 2.77, 3.02 (together 2H, 4dd, J3.3, 16.2; 4.7, 15.3; 7.9, 15.2; 9.4, 16.3Hz), 3.37 and 3.41, 3.45 (together 2H, ABq, s, J14.7Hz), 3.69-3.95 (2H, m), 4.16-4.36 (1H, m), 4.58 (2H, s), 4.99, 5.00(together 1H, 2d, J4.8, 4.7Hz), 5.57 (1H, dd, J4.8, 8.8Hz), 6.93-7.07 (3H, m) 7.28-7.36 (2H, m), 7.45,7.56 (together 1H, 2d, J8.8Hz).

(d) t-Butyl (RS)-2-Hydroxy-2-[(3R,4R)-3-phenoxyacetamido-4-[2-oxo-3-[(RS)-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-on-1-yl]acetate

The azetidinone prepared in Example 1(c), (2.37g) in dichloromethane (10mls) was treated successively with 0.5M t-butyl glyoxylate in 1,2-dichloroethane, (13ml) and triethylamine (87µl). The reaction was monitored by t.l.c. analysis (ethyl acetate) until no more starting material remained. The solution was concentrated to a small volume and flash chromatographed on silica gel, eluting with 80% ethyl acetate in hexane. The title compound was obtained as a colourless foam as a mixture of diastereoisomers, (2.65g, 83%); $\nu_{max}(CH_2Cl_2)$ 3492, 3405, 1782, 1735 and 1696cm^{-1}; $\delta_H(CDCl_3)$ 1.38-1.50 (1H, m), 1.54 (9H, s), 1.83-1.95 (2H, m), 2.01-2.10 (1H, m), 2.56-2.89 (2H, m), 3.48-3.64 (2H, m), 3.68-3.80 (1H, m), 3.82-3.92 (1H, m), 4.13-4.24 (1H, m), 4.49-4.55 (1H, m), 4.59 (2H, s), 5.03-5.13 (1H, m), 5.26-5.58 (2H, m), 6.94-7.07 (3H, m), 7.30-7.46 (2H, m) and 7.48, 7.44,7.54, 7.65 (together 1H, 4d, J8.8Hz).

(e) t-Butyl 2-[(3R,4R)-3-Phenoxyacetamido-4-[2-oxo-3-[(RS)-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-on-1-yl]-2-tri-n-butylphosphoranylideneacetate

t-Butyl 2-hydroxy-2-[(3R,4R)-3-phenoxyacetamido-4-[2-oxo-3-[(RS)-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-on-1-yl]acetate, (2.622g) in dry THF (10ml) was cooled to -20°C under argon. Lutidine (0.828g, 0.898ml) was added followed by the dropwise addition of a solution of thionyl chloride (0.921g, 0.557ml) in THF (5ml). A white precipitate was formed which slowlychanged to yellow on warming to 0°C. T.l.c. analysis (ethyl acetate) showed loss of starting material. The reaction mixture was filtered and the solid washed with THF. The solvent was removed from the filtrate

and the residue dissolved in toluene. Re-evaporation gave the crude chloride as a brown gum. This was taken up in dioxan (20ml, dried by eluting through alumina), and treated with tri-n-butylphosphine (2.29g, 2.82ml) at ambient temperature for 0.25h. T.l.c. analysis showed formation of product, the solution was diluted with ethyl acetate and washed with water (3x), brine and then dried. Removal of solvent followed by flash chromatography of the residue gave the title compound as a brown gum, (1.726g, 48%); $\nu_{max}(CH_2Cl_2)$ 3412, 1764, 1690, 1627 and 1601cm^{-1}; [mass spectrum: +ve ion (thioglycerol) MH^+(693)].

(f) t-Butyl (6R,7R)-7-Phenoxyacetamido-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

t-Butyl 2-[3R,4R-3-phenoxyacetamido-4-[2-oxo-3-[(RS))-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-on-1-yl]-2-tri-n-butylphosphoranylidene acetate, (1.726g) in dry toluene (40 ml) was heated under reflux, under argon overnight. T.l.c. analysis showed loss of starting material with formation of a less polar product. The solution was concentrated and flash chromatographed to give a diastereoisomeric mixture of the title compound as a crisp, pale yellow foam, (0.9g, 76%); $\nu_{max}(CH_2Cl_2)$ 3406, 1782, 1714 and 1697cm^{-1}; $\delta_H(CDCl_3)$ 1.54 (10H, s, overlapping m), 1.82-2.17 (3H, m), 2.13, 2.52 (together 1H, 2dd, J9.4, 13.4; 7.0, 13.7Hz), 2.82, 3.04 (together 1H, 2dd, J2.7, 13.3; 4.5, 13.8Hz), 3.41 and 3.63, 3.48 and 3.74 (together 2H,2ABq, J18.3, 18.1Hz), 3.70-4.17 (3H, m), 4.56, 4.67 (together 1H, 2s), 5.00, 5.03 (together 1H, 2d, J5.1, 4.9Hz), 5.85, 5.89 (together 1H, 2dd, J4.8, 9.1; 4.8, 8.8Hz), 6.92-7.70 (3H, m) and 7.26-7.37 (3H, m). [Mass spectrum: +ve ion (3-nitrobenzyl alcohol, sodium acetate) MNa^+(497)].

(g) t-Butyl (6R,7R)-7-Amino-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

t-Butyl (6R,7R)-7-phenoxyacetamido-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate, (0.87g) in dry dichloromethane (5ml), was cooled to -20°C under argon. N-methylmorpholine (0.408g, 0.443ml) was added followed by a solution of phophorus pentachloride (0.497g) in dry dichloromethane (12.4ml). The solution was stirred at -20°C for 30 mins and then methanol (5ml) was added in one portion. The solution was allowed to warm to ambient temperature over 1h, and then water (5ml) was added. The reaction was then vigorously stirred for a further 30 minutes. The dichloromethane was removed in vacuo and the residue diluted with ethyl acetate. The pH was adjusted to 7 with 0.880 ammonia. The organic phase was washed with water, brine and dried. Removal of solvent and flash chromatography afforded the title compound as a mixture of diastereoisomers, as a yellow gum, (0.443g, 71%); (Found: M^+, 340.1461. $C_{16}H_{24}N_2O_4S$ requires M, 340.1457); $\nu_{max}(CH_2Cl_2)$ 3409(w), 1775 and 1716cm^{-1}; $\delta_H(CDCl_3)$ 1.53 (10H, s overlapping m), 1.80-2.14 (3H, m), 2.37, 2.52 (together 1H, 2dd, J9.0, 13.3; 6.8, 13.7Hz), 2.74, 2.99 (together 1H, 2dd, J3.0, 13.5; 4.8, 13.8Hz), 3.38-4.24 (5H, m), 4.70 (1H, d, J4.9Hz), 4.94,4.96 (together 1H, 2d, J5.1, 5.0Hz).

(h) t-Butyl (6R,7R)-7-[2-(Z)-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

2-(Z)-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid hydrochloride (0.664g), as a suspension in dry DMF (4ml), under argon was cooled to -50°C and treated with N,N-diisopropylethylamine (0.357g, 0.481ml) followed by methanesulphonyl chloride, (0.159g, 0.107ml). After 1h at

-50°C the homogeneous solution was treated with the amino cephalosporin from (g), (0.428g) and pyridine (0.099g, 0.101ml) in DMF (5ml). The reaction mixture was allowed to warm to ambient temperature over 1h, and then diluted with ethyl acetate, washed with water and brine and dried. The solvent was removed in vacuo and the residue flash chromatographed to give a diastereoisomeric mixture of the title compound as a pale yellow foam, (0.727g, 76%) $\nu_{max}(CH_2Cl_2)$ 3397, 1782, 1718 and 1686cm^{-1}; $\delta_H(CDCl_3)$, 1.52 (10H, s overlapping m), 1.80-2.16 (3H, m), 2.33, 2.51 (together 1H, 2dd, J9.3, 13.3; 7.0, 13.7Hz), 2.80, 3.04 (together 1H, 2dd, J2.7, 13.4; 4.5, 13.7Hz), 3.37-3.89 (5H, m), 4.05 (3H, s), 5.02, 5.04 (together 1H, 2d, J4.9, 4.6Hz), 5.87 (1H, m) 6.74 (1H, s), 6.87 (1H, d, J8.7Hz, exchangeable), 7.04 (1H, s, exchangeable) and 7.31 (15H, s). [Mass spectrum: +ve ion (3-Nitrobenzyl alcohol, sodium acetate) MNa$^+$ (788)].

(i) Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

t-Butyl (6R,7R)-7-[2-(Z)-methoxyimino-2-(2-tritylamino-thiazol-4-yl)acetamido]-3-[(RS)-tetrahydrofuran-2-yl-methyl]ceph-3-em-4-carboxylate, (0.677g) was dissolved in 0.1M hydrochloric acid in 90% formic acid (8.9ml). After 1h at ambient temperature, concentrated hydrochloric acid, (0.2ml) was added and the reaction continued for a further 0.5h. The white precipitate was filtered off and washed with a little formic acid. The formic acid was removed in vacuo from the filtrate to give a colourless, solid residue. Water (5ml) was added and the pH adjusted to 7 with sodium bicarbonate solution. The slightly turbid solution was eluted through a column of HP20SS, with 1,2,4,6 and 8% THF in water. The fractions containing the title compound, (by h.p.l.c. analysis) were combined, concentrated and

freeze-dried to give a colourless solid, (0.346g, 80%); ν_{max}(KBr) 1757, 1670, 1597 and 1532cm^{-1}; δ_H[$(CD_3)_2SO$] 1.40-1.59 (1H, m), 1.64-1.88 (3H, m), 2.20-2.34 (1H, m), 2.67, 3.04 (together 1H, 2dd, J4.4, 13.0; 6.8, 13.2Hz), 3.12-3.60 (3H, m,), 3.68-4.02 (5H, m overlapping s at 3.83), 4.94, 4.96 (together 1H, 2d, J4.6Hz), 5.49 (1H, dd, J4.7, 8.1Hz), 6.74 (1H, s), 7.26 (2H, s, exchangeable) and 9.50 (1H, d, J8.1Hz, exchangeable). [Mass spectrum: +ve ion (thioglycerol) MH^+ (490)].

Example 2

Pivaloyloxymethyl (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

Pivaloyloxymethyl bromide (0.176g) in acetone (3ml) and sodium iodide (0.135g), under argon were reacted together at room temperature for 0.5h. The acetone was evaporated and replaced with N-methylpyrrolidinone (3ml). This suspension was added to a suspension of sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate (0.2g) in N-methylpyrrolidinone (3ml). After 1h the solution was diluted with ethyl acetate, washed with water, brine and then dried. After removal of solvent, flash chromatography on silica gel eluting with ethyl acetate, afforded the title compound as a pale yellow foam (0.086g, 36%); ν_{max} (CH_2Cl_2) 3480, 3391, 1786, 1750, 1687 and 1607cm^{-1}; δ_H ($CDCl_3$) 1.24 and 1.25 (9H, 2s), 1.43-2.18 (4H, m's), 2.32 and 2.34 (1H, 2dd's, J 9.3, 13.3 and 7.5, 13.7Hz), 2.87 and 3.13 (1H, 2dd's, J 2.5, 13.3 and 3.8, 13.7Hz), 3.47-4.17 (8H, m's overlapping s, 4.12), 5.05 and 5.09 (1H, 2d's, J 4.7 and 4.7Hz), 5.85-5.97 (3H, m), 6.33 (1H, br. s), 7.02 and 7.03 (1H, 2s's), 7.48 and 7.55 (1H, 2d's, J 8.7 and 8.8Hz). [Mass spectrum: +ve ion (3NOBA, Na^+) MH^+ (582), MNa^+ (604)].

In Vitro Biological Data

MIC (µg/ml)

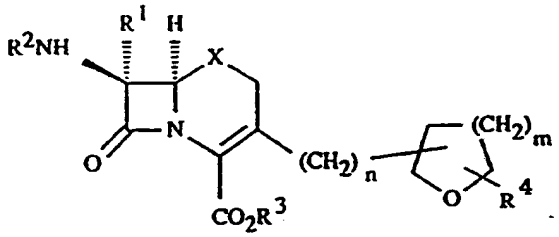
	Organism	
	E. coli (NCTC 10418)	S. Aureus (Oxford)
Example 1	1.0	2.0

In Vivo Biological Data

Peak serum concentration of the compound from Example 1 was 33.0 µg/ml, obtained at 30 minutes following oral dosing of the compound from Example 2 to mice at a dose equivalent to 50 mg/kg.

Claims

1. A compound of formula (I) or a salt thereof:



wherein

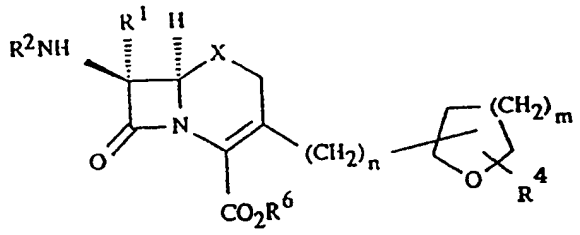
R^1 is hydrogen, methoxy or formamido;

R^2 is an acyl group;

CO_2R^3 is a carboxy group or a carboxylate anion, or R^3 is a readily removable carboxy protecting group;

R^4 represents up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent; X is S, SO, SO_2, O or CH_2; m is 1 or 2; and n is 1, subject to the proviso that when R^1 is hydrogen, X is S and the 3-position substituent is unsubstituted tetrahydropyran-2-ylmethyl (m=2), then, when R^3 is hydrogen, R^2 is not 2-thienylacetyl or D-α-aminophenylacetyl, and when R^3 is t-butyl, R^2 is not 2-thienylacetyl, D-α-aminophenylacetyl or N-t-butoxycarbonyl-D-α-amino-phenylacetyl.

2. A compound as defined in claim 1 having the formula (Ia):



(Ia)

wherein R^1, R^2, R^4, m, n and X are as defined with respect to formula (I) in claim 1 and the group CO_2R^6 is CO_2R^3 where CO_2R^3 is a carboxy group or a carboxylate anion, or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, other than 3-(2-tetrahydropyranylmethyl)-7-(2-thienylacetamido)-3-cephem-4-carboxylic acid or 3-tetrahydropyranylmethyl)-7β-(D-α-phenylglycyl)aminoceph-3-em-4-carboxylic acid.

3. An in vivo hydrolysable ester of a compound of formula (Ia) as defined in claim 2.

4. A compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as defined in claim 2, other than 3-(2-tetrahydropyranylmethyl)-7-(2-thienylacetamido)-3-cephem-4-carboxylic acid or 3-(2-tetrahydropyranylmethyl)-7β-(D-α-phenylglycyl)aminoceph-3-em-4-carboxylic acid, for use as a therapeutic agent.

5. An in vivo hydrolysable ester of a compound of formula (Ia) as defined in claim 3 for use in the oral treatment of bacterial infections.

6. A pharmaceutical composition comprising a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as claimed in claim 2, and a pharmaceutically acceptable carrier.

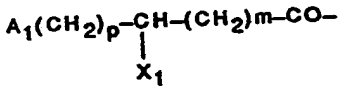
7. An orally administrable pharmaceutical composition comprising an in vivo hydrolysable ester of a compound of formula (Ia), as defined in claim 3, and a pharmaceutically acceptable carrier.

8. A method of treating bacterial infections in humans and animals comprising orally administering a therapeutically effective amount of an in vivo hydrolysable ester of a compound of formula (Ia) as defined in claim 3.

9. The use of an in vivo hydrolysable ester of a compound of formula (Ia), as defined in claim 3, for the manufacture of a medicament for the oral treatment of bacterial infections.

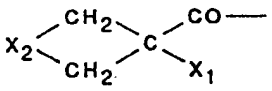
10. A compound as claimed in claim 1, 2 or 3 wherein R^1 is hydrogen.

11. A compound as claimed in claim 1, 2 or 3 wherein R^2 is an acyl group of formula (a) to (f):

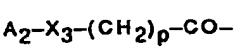


(a)

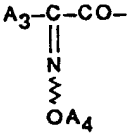
(b)



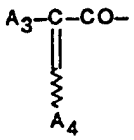
(c)



(d)



(e)



(f)

wherein p is 0, 1 or 2; m is 0, 1 or 2; A_1 is C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-6} cycloalkyl, cyclohexenyl, cyclohexadienyl, an aromatic or heteroaromatic group; X_1 is a hydrogen or halogen atom, a carboxylic acid, carboxylic ester, sulphonic acid, azido, tetrazolyl, hydroxy, acyloxy, amino, ureido, acylamino, heterocyclylamino, guanidino or acylureido group; A_2 is an aromatic or heteroaromatic group, a substituted alkyl group; or a substituted dithietane; X_2 is a $-CH_2OCH_2-$, $-CH_2SCH_2-$ or alkylene group; X_3 is an oxygen or sulphur atom; A_3 is an aryl or heteroaryl group; and A_4 is hydrogen, C_{1-6}alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-6})alkyl, C_{1-6} alkoxycarbonyl(C_{1-6}) alkyl, C_{2-6} alkenyl, carboxy(C_{1-6})alkyl, C_{2-6} alkynyl, aryl or C_{1-6}alkyl substituted by up to three aryl groups.

12. A compound as claimed in claim 11 wherein A_1 is optionally substituted phenyl, X_1 is hydrogen or amino, A_2 is optionally substituted phenyl, X_3 is oxygen , A_3 is

aminothiazolyl, aminothiadiazolyl or furyl, and A_4 is hydrogen, C_{1-6} alkyl, or carboxy C_{1-6} alkyl.

13. A compound as claimed in any one of claims 3, 10, 11 or 12 wherein R^3 is pivaloyloxymethyl.

14. A compound as claimed in any one of claims 3 and 10 to 13 wherein the cyclic ether group bonded to the 3-position of the cephalosporin nucleus is unsubstituted or substituted by up to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoyloxy C_{1-6} alkyl or C_{1-6} alkoxy C_{1-6} alkyl.

15. A compound as claimed in any one of claims 1 to 3 and 10 to 14 wherein m is 1.

16. A compound as claimed in any one of claims 1 to 3 and 10 to 14 wherein the cyclic ether group is a tetrahydrofuran-2-yl or a tetrahydropyran-2-yl group.

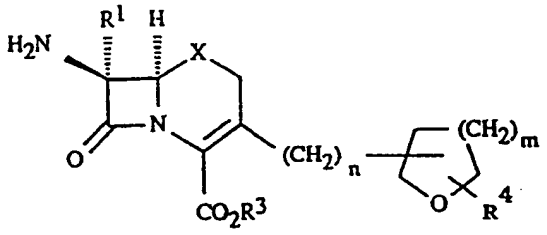
17. Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]-ceph-3-em-4-carboxylate.

18. Pivaloyloxymethyl (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate.

19. A compound of formula (I) as defined in claim 1 substantially as hereinbefore described with reference to the preparative examples.

20. A process for the preparation of a compound of formula (I) as defined in claim 1 which process comprises:

(a) treating a compound of formula (II) or a salt thereof:



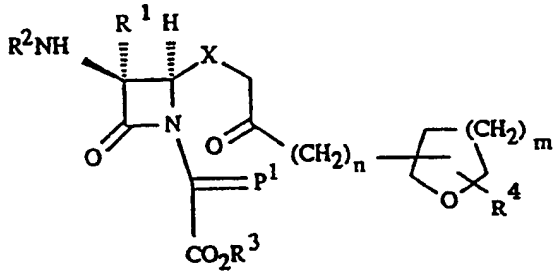
(II)

wherein R^1, CO_2R^3, R^4, m, n, and X are as hereinbefore defined with respect to formula (I) in claim 1, wherein any reactive group may be protected, and wherein the amino group is optionally substituted with a group which permits acylation to take place, with an N-acylating derivative of an acid of formula (III):

$$R^2OH \qquad \text{(III)}$$

wherein R^2 is as hereinbefore defined with respect to formula (I) in claim 1 and wherein any reactive group may be protected; or

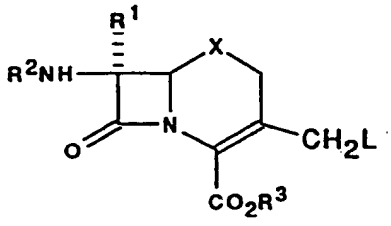
(b) cyclising a compound of formula (IV):



(IV)

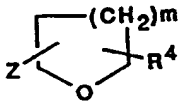
wherein X, R^1, R^2, R^4, m, n and CO_2R^3 are as hereinbefore defined with respect to formula (I) in claim 1 and P' is a phosphorus residue; or

(c) treating a compound of formula (X):



(X)

wherein R^1, R^2, CO_2R^3 and X are as hereinbefore defined with respect to formula (I) in claim 1, and L is a leaving group, with a compound of formula (XI):



(XI)

wherein Z is an organo-cuprate group and R^4 and m are as hereinbefore defined with respect to formula (I) in claim 1;

and thereafter, if necessary or desired, carrying out one of the following steps:

i) removing any protecting groups;

ii) converting the group CO_2R^3 to a different group CO_2R^3;

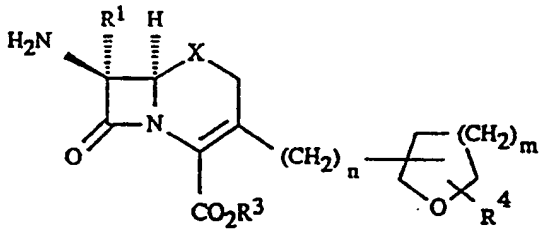
iii) converting the group R^2 to a different group R^2;

iv) converting the group X to a different group X;

v) converting the product into a salt.

21. A process for the preparation of a compound of formula (I) substantially as hereinbefore described in the preparative Examples.

22. A compound of formula (II) or a salt thereof:



(II)

wherein R^1 CO_2R^3, R^4, X, m and n are as hereinbefore defined with respect to formula (I) in claim 1.

23. t-Butyl 6R,7R-7-Amino-3-(tetrahydrofuran-2-ylmethyl)-ceph-3-em-4-carboxylate.

24. A compound of formula (II) as defined in claim 22 substantially as hereinbefore described with reference to the preparative Examples.

25. A pharmaceutical composition as claimed in claim 6 or 7 further comprising a β-lactamase inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01227

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 501/20 C 07 D 501/18 A 61 K 31/545
C 07 D 463/00 C 07 D 498/053

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 501/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	FR,A,2166356 (BEEHAM GROUP LTD) 17 August 1973, see pages 51-53; example 7 ---	1-25
A	EP,A,0359536 (BEECHAM GROUP PLC) 21 March 1990, see pages 23-31; claims ---	1-25
A	FR,A,2166355 (BEECHAM GROUP LTD) 17 August 1973, see pages 51-53; example 7, & GB1405758, (cited in the application) --- -/-	1-25

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08-10-1991	04. 11. 91
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: O. Toribio Nuria TORIBIO

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Journal of Medicinal Chemistry,, vol. 20, no. 8, August 1977, American Chemical Society, (Washington, US), Edward G. Brain et al.:"Structure-activity relationships in cephalosporins prepared from penicillins. 2. Analogues of cephalexin substituted in the 3-methyl group", pages 1086-1090, see page 1088, table IV, compounds 35,36, (cited in the application)	1-25

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1] (partially)

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers 1-25 because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

The search has been systematically perfomed for the compounds of formula I and II as far as X represents S and its oxides (the only examples described)

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101227 SA 49540

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 24/10/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A- 2166356	17-08-73	GB-A-	1405757	10-09-75
		AT-B-	333948	27-12-76
		AU-A-	4856472	09-05-74
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		JP-B-	60040235	10-09-85
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		JP-A-	58095480	07-06-83
		JP-B-	60040234	10-09-85
		NL-A-	7215297	05-07-73
		US-A-	3939157	17-02-76
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